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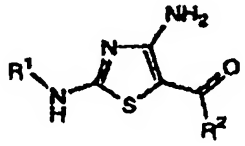
19 August 1999 (19.08.99)

(54) Title: 4-AMINOTHIAZOLE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS INHIBITORS OF CYCLIN-DEPENDENT KINASES




(I)

(57) Abstract

This invention is directed to aminothiazole compounds of formula (I) wherein $R^1$ is a substituted or unsubstituted group selected from: $C_{1-6}$-alkyl; $C_{1-6}$-alkenyl; $C_{1-6}$-alkynyl; $C_{1-6}$-alkoxyl; $C_{1-6}$-alcohol; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, cycloalkyl; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, aryl; carbonyl; ether; ($C_{1-6}$-alkyl)-carbonyl; ($C_{1-6}$-alkyl)-aryl; ($C_{1-6}$-alkyl)-cycloalkyl; ($C_{1-6}$-alkyl)-($C_{1-6}$-alkoxyl); aryl-($C_{1-6}$-alkoxyl); thioether; thiol; and sulfonyl; wherein when $R^1$ is substituted, each substituent independently is a halogen; haloalkyl; $C_{1-6}$-alkyl; $C_{1-6}$-alkenyl; $C_{1-6}$-alkynyl; hydroxyl; $C_{1-6}$-alkoxyl; amino; nitro; thiol; thioether; imine; cyano; amido; phosphonato; phosphine; carboxyl; thiocarbonyl; sulfonyl; sulfonamide; ketone; aldehyde; ester; oxygen; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, cycloalkyl; or carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, aryl; and $R^2$ is a carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure having a substituent at the position adjacent to the point of attachment, which ring structure is optionally further substituted, where each substituent of $R^2$ independently is a halogen; haloalkyl; $C_{1-6}$-alkyl: $C_{1-6}$-alkenyl; $C_{1-6}$-alkynyl; hydroxyl; $C_{1-6}$-alkoxyl; amino; nitro; thiol; thioether; imine; cyano; amido; phosphonato; phosphine; carboxyl; thiocarbonyl; sulfonyl; sulfonamide; ketone; aldehyde; ester; oxygen; carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, cycloalkyl; or carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, aryl; or a pharmaceutically acceptable salt of a compound of formula (I), or a prodrug or pharmaceutically active metabolite of a compound of formula (I) or pharmaceutically acceptable salt thereof, for inhibiting cyclin-dependent kinases (CDKs), such as CDK1, CDK2, CDK4, and CDK6. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compositions containing such compounds and to methods of treating malignancies and other disorders by administering effective amounts of such compounds.

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/22809

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/42 A61K31/425 C07D417/12 A61K31/44 C07D277/56
C07D417/06 C07D417/14 A61K31/47 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 92 20642 A (RHONE-POULENC RORER INTERNATIONAL (HOLDINGS) INC.) 26 November 1992 see claims 1-4,7 --- | 1-14,16, 17 |
| Y | WO 95 15758 A (RHONE-POULENC RORER PHARMACEUTICALS INC.) 15 June 1995 see claims 1-3,6,7 --- | 1-14,16, 17 |
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| P,X | WO 98 33798 A (WARNER LAMBERT COMPANY) 6 August 1998 cited in the application see claims 1-3,9,20,21,26-36 --- -/-- | 1-4,14, 17 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 10 June 1999 | 18. 06. 99 |

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|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Hartrampf, G |

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/22809

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| A | RAJASEKHARAN K.N. ET AL.: "Studies on the synthesis of 5-acyl-2,4-diaminothiazoles from amidinothioureas" SYNTHESIS, vol. 5, 1986, pages 353-355, XP002095704 see compounds 4a-4g and 4i-4m --- | 1-13,16 |
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| A | JENARDANAN G.C. ET AL.: "1-(N-Arylthiocarbamoyl)amidino-3,5-dimethylpyrazoles - preparation and use in heterocycle synthesis" SYNTHETIC COMMUNICATIONS, vol. 27, no. 19, 1997, pages 3457-3462, XP002095706 see compounds 5a - 5e, page 3458 --- | 1-13,16 |
| P,A | BINU R. ET AL.: "Synthesis and cyclization of 1-(N-nitroamidino)thioureas to 2,4-diaminothiazoles" ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL, vol. 30, no. 1, 1998, pages 93-96, XP002095707 see compounds 4a - 4h, page 94 ----- | 1-13,16 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/22809

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [X] Claims Nos.: 1-14,16,17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-12, 13 (partially), 14

   Compounds of formula (I) wherein R2 is a carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure having a substituent at the position adjacent to the point of attachment and pharmaceutical compositions containing them

2. Claims: 13 (partially), 16, 17

   Compounds of formula (I) wherein R1 is a certain benzenesulfonamide group and R2 is a substituted or unsubstituted carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure and pharmaceutical compositions containing them

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-14,16,17

The claims contain the expression "pharmaceutically active metabolite" which is considered to be a functional feature and renders the scope of the claims ambiguous. Due to such a definition the compounds of formula (I) encompass too broad a range of different chemical groups, not supported by any examples in the descriptive part of the application. Thus claims 1 to 14, 16 and 17 are considered to be insufficiently substantiated by the description, cf. Article 6 PCT.
The vast number of theoretically conceivable compounds resulting from claims drafted in such an ambiguous way precludes a comprehensive search. Thus the search should not be considered to cover any pharmaceutically active metabolites of the compounds of formula (I).

A further ambiguity arises since some of the examples, see e.g. compounds A(1) - A(4), A(8), A(12), B, C(1) - C(3), C(6), C(18), C(30), C(31), D(1), D(2), D(4), I(6) - I(17) and I(19) - I(23) are obviously not covered by the present claims. Although explicitly made and tested for inhibitory activity of cyclin-dependent kinases, they do neither contain the mandatory ortho-substitution of radical R2 (see claim 1 to 12, 13 and 14), nor the benzenesulfonamide moiety for radical R1 (see claims 13, 16 and 17) which otherwise could be considered to be the distinguishing feature in comparison to the prior art.

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/US 98/22809

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